Managing treatment-resistant depression: what do the guidelines say?

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Abstract

Numerous approaches have been used to define and stage treatment-resistant depression (TRD) as well as to find predictors of treatment outcome. Nevertheless, TRD remains a complex disorder, with high morbidity and mortality. This paper briefly reviews current guidelines for managing TRD, summarising the best pharmacological strategies and 'next steps' of psychological and physical treatments. When depressed patients fail to remit after two or more conventional antidepressant treatments, combined approaches, targeting multiple molecular, psychological and physical mechanisms, seem to be the most effective strategy.

Keywords: treatment-resistant depression, antidepressants, combined approaches, somatic therapies, predictors

1. Introduction

Despite pharmacotherapy being effective in more than half of all depressed patients, between 20% and 30% fail to respond to any available antidepressant (AD) treatment, and around 50% have treatment-resistant depression (TRD) defined, in broader terms, as failure to respond to two or more adequate trials of AD monotherapy (1). A universally accepted definition for TRD does not currently exist, as several staging models have tried to define the minimum criteria for dose and duration of (failed) therapies required to meet such a definition (2). More recently, a multidimensional model has been developed that also considers depression severity and duration as relevant criteria for TRD (3).

Research in the last few years has identified early clinical and biological predictors of poor response, which could be theoretically used to personalize treatment practice and escalate sooner the identified patients through more assertive treatment algorithms developed for TRD. The most commonly replicated clinical predictors of TRD include comorbid anxiety disorder, current suicidal risk, and bipolarity (4). Moreover, response to ADs has been explored in terms of brain structures, neurotransmission, and molecular targets. PET and MRI studies of subjects before starting AD treatment have found that non-responders have lower activity in the rostral anterior cingulate cortex, lower metabolism in the amygdala and thalamus, higher metabolism in the prefrontal cortex, and reduced fronto-limbic and hippocampal grey matter (5). Molecular predictors of TRD include the short allele of the serotonin transporter coding sequence (6), the Met allele of the Val/Met (rs6265) polymorphism in the brain-derived neurotrophic factor (BDNF) gene, impaired hypothalamic-pituitary-adrenal axis (HPA) (7, 8), as well as increased levels of blood protein and mRNA inflammatory biomarkers (9, 10).

This paper provides a concise overview of the most recent and updated guidelines for treating TRD. It is mainly based on the latest revision of the British Association for Psychopharmacology (BAP) Guidelines for Treating Depressive Disorders (2015) (11) and on the 2018 edition of the Maudsley Prescribing Guidelines (12). These two guidelines, in turn, extensively cross-reference other international evidence-based guidelines, such as from NICE (National Institute for Health and Care Excellence) (2015 and 2017) , the Cochrane Database, the American Psychiatric Association (2010) (13), the World Federation of Societies of Biological Psychiatry (14), the Canadian Network for Mood and Anxiety Treatment (15), as well as the

results of the STAR*D research program (Sequenced Treatment Alternatives to Relieve Depression) (16).

2. First-choice interventions

Most studies indicate that a chosen treatment strategy has failed when there is no improvement after 4-6 weeks. According to the BAP guidelines, both switching AD and augmentation (adding another agent to the AD) are evidence-based next steps. There is limited evidence that increasing the dose could be effective, but it should be considered if there are minimal adverse effects and/or there has been some improvement on the AD. This may be particularly effective for ADs with a putative dose response, such as tricyclic antidepressants (TCAs), venlafaxine and escitalopram (but not for other selective serotonin reuptake inhibitors (SSRIs)). Both the BAP and the Maudsley guidelines do not specify whether switching or augmentation should be preferred. However, switching, in particular, switching within the same drug class, is generally less supported by literature (2017 NICE draft guidelines (17)).

The best options for both switching and augmentation are described below.

2.1 Switching

Switching should take place after 1-2 weeks if adverse effects are not tolerable and after 3-4 weeks if no improvement at all is seen.

BAP guidelines suggest:

- switching from an SSRI to venlafaxine gives a significant advantage compared with switching to another SSRI. Higher doses of venlafaxine (mean 309 mg) versus standard are associated with faster and greater response, but poorer tolerability
- after inadequate response to initial AD therapy (SSRI or serotonin norepinephrine reuptake inhibitor (SNRI)), switching to vortioxetine (10-20 mg/day) is more effective than to agomelatine (25-50 mg/day)
- in most cases, cross-tapering during switching is the preferred option. However, direct switching (without washout) from initial SSRI to another SSRI, nortriptyline, mirtazapine, buproprion, reboxetine, venlafaxine and duloxetine, appears well tolerated, unless the initial drug has long-lasting effects (e.g. from fluoxetine to TCA). This evidence is supported also by the Maudsley guidelines, as it may reduce the risk of discontinuation symptoms.

The Maudsley guidelines report switching to mirtazapine (30-45 mg/day) and to venlafaxine (200 mg/day) as the most supported strategies.

2.2 Augmentation and combination strategies

Antipsychotics

BAP guidelines report higher remission and response rates with the following:

- quetiapine (XR, 150-300 mg/day): is effective with SSRI, SNRI, buproprion or amitriptyline, and is superior to lithium augmentation, but it is associated with more metabolic abnormalities;
- aripiprazole (2-20 mg/day);
- risperidone (0.5-3 mg/day);
- olanzapine (6.25-12.5 mg/day): this is often added to fluoxetine (25-50 mg/day), although the BAP guidelines found this association less effective than adding other antipsychotics. In contrast, the Maudsley and the NICE guidelines highlight combined olanzapine and fluoxetine as very effective, especially in bipolar depression.

Lithium

Although disappointing results were obtained in the STAR*D study, lithium augmentation of SSRI is recommended by BAP guidelines. However, it should be maintained for at least 1 year to prevent early relapses. As also confirmed by the Maudsley guidelines, it is more effective when plasma levels above

0.6mmol/L are achieved.

Thyroid hormone

Although T3 (20-50 µg) was better tolerated than lithium in the STAR*D study, both BAP and Maudsley guidelines report some negative evidence. The use of thyroid hormone usually needs specialist referral and it is considered a second choice option.

Antidepressant combination

The most common combinations recommended by BAP are:

- SSRI with mirtazapine, reboxetine, bupropion or a TCA;
- mirtazapine with TCA or venlafaxine;
- mianserin with a TCA or SSRI (less supported).

The Maudsley guidelines suggest combining bupropion (up to 400 mg/day) with an SSRI, or venlafaxine with mianserin (30 mg/day) or mirtazapine (30-45 mg/day), while combining an SSRI with a TCA is considered as last choice, because of the potential adverse effects. Combining buspirone (up to 60 mg/day) is less effective than buproprion according to STAR*D, and thus it is considered as second choice by both guidelines.

Anticonvulsants

Adding lamotrigine (100-400 mg/day) is less supported by BAP guidelines but especially recommended for treating bipolar depression in Maudsley guidelines and considered the best tolerated augmentation strategy (18).

Psychostimulants

These drugs have been found to reduce fatigue, promote wakefulness and to elevate mood with a faster effect (few hours) when compared with ADs. Intravenous ketamine (0.5 mg/kg over 40 minutes) has a very rapid response and high remission rates; it is well tolerated at sub-anaesthetic dose, even though cognitive effects such as confusion and dissociation are occasionally reported, and repeated infusions are necessary to maintain the effect (evidence supported by both guidelines). In the near future, intranasal esketamine may become available and supplant the intravenous form (19). Fewer data are available for modafanil and methylphenidate. Modafanil (200 mg/day) has proven effective as adjunctive therapy for depression-related hypersomnia and fatigue, and seems not to induce tolerance, dependence or psychosis, but lacks the euphoric effect of amphetamines. Methylphenidate is less supported by the BAP guidelines while the Maudsley guidelines report a clear effect in decreasing fatigue when added to SSRIs.

Others

There are preliminary results of efficacy for augmentation with oestrogens, testosterone and with S-adenosyl methionine (SAMe), although the latter has been weakly supported by a Cochran review (20). Moreover, many other pharmacological treatments have been reported in the literature, but the evidence is sparse: both the BAP and the Maudsley guidelines report adding tryptophan (2-3 g tds), pindolol (5 mg tds or 7.5 mg once daily) and omega-3-triglycerides augmentation, as the best supported.

3. Other approaches

3.1 Combination with psychotherapies

In TRD it may also be appropriate to add psychotherapy. The STAR*D study reported no difference in overall outcome between cognitive behaviour therapy (CBT) and medication augmentation or switch, although medication augmentation worked faster. According to the BAP guidelines, addition of CBT to pharmacological medication in patients with residual symptoms resulted in greater remission rates than pharmacological treatment alone. Moreover, there is evidence that switching to another SSRI is more effective when combined with CBT (21). Alternatively, other psychological or behavioural treatments can

be considered, such as Behavioural Activation and Interpersonal Psychotherapy, which are more effective during acute relapses (22).

3.2 Somatic therapies

For patients who have failed numerous treatments, somatic therapies are valuable options (23). Although new physical treatments are available, electroconvulsive therapy (ECT) is considered the gold standard, with a 60% to 90% rate of acute response in TRD; a number of previous reports expressed concerns about acute cognitive impairment, lasting up to few days, but a recent study showed no such evidence (24).

Transcranial Magnetic Stimulation (TMS) is a well-tolerated non-invasive technique, which aims to stimulate the cerebral cortex through magnetic fields applied at the skull surface. There is no evidence of cognitive impairment. Repetitive (r)TMS efficacy is analysed in the BAP guidelines and in NICE guidance (2015) (25): in summary, it is effective in TRD, although it is inferior to ECT, especially in psychotic depression, and patients often require additional rTMS courses and pharmacological treatments.

Vagus Nerve Stimulation (VNS) and Deep Brain Stimulation (DBS) represent novel but more invasive treatments. VNS requires implantation in the left chest wall of a pacemaker-like device which regularly stimulates the vagus nerve. VNS is not indicated for acute depressive exacerbations and could have adverse effects related to stimulation of recurrent laryngeal nerves. Effects are evident after some months; it appears to be effective in patients with major depressive disorder (MDD) or bipolar II disorder of low to moderate severity but not in severe TRD, especially if patients have failed multiple AD strategies (26). It can usually be combined with ADs or with ECT in case of acute relapse.

DBS is a reversible neurosurgical procedure, consisting of implanting electrodes at specific brain anatomical locations and delivering an electrical impulse of variable intensity and frequency. DBS efficacy in TRD is supported by some studies, with most targeted brain areas being the subgenual cingulate, the ventral anterior cingulate, the nucleus accumbens, the substantia innominata and the medial forebrain bundle. However, it should still be considered experimental at present (27). In addition, there are many reports that discontinuation of DBS may produce a rapid return of symptoms or induce suicide attempts.

4. Conclusion

When individuals with MDD fail to achieve remission after conventional pharmacotherapy, multiple approaches seem to be more effective than a single treatment; both pharmacological combinations and augmentation remain popular treatment strategies, with the most robust evidence supporting combining ADs or adding atypical antipsychotics. Moreover, there are numerous studies supporting somatic neurostimulatory modalities. Ongoing clinical trials are exploring the efficacy of novel compounds, targeting glutamate, inflammatory and metabolic/oxidative pathways, as well as buprenorphine, riluzole and intranasal esketamine. Moreover, many researchers are trying to identify baseline predictors of adverse treatment outcome, in order to achieve the early detection of depressed patients at greater risk of poor response and thus escalate the treatment protocols using a personalised approach.

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